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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/908,453	08/07/97	RUVKUN G	084277/04002

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EXAMINER	
SHUKLA, R	

ART UNIT	PAPER NUMBER
1632	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/908,453	Applicant(s) Ruvkun et al
	Examiner Ram Shukla	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-28* is/are pending in the application.

Of the above, claim(s) *1-7, 14, and 21-28* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *8-13 and 15-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3, 4, &10*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Amendment filed on 7-26-99 (Paper No. 15) is entered.

2. Claims 8-13 and 15-20 are pending in the instant application.

3. Claims 1-4, 14, and 21-28 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 15.

4. The instant application claims priority to US provisional application, Serial No. 60/023,382 filed on 8-7-96.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 8 and 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the interim guidelines on written description published June 15, 1998 in the Federal Register at Volume 63, Number 114, pp 32639-32645 (also available at www.uspto.gov).

Claim 8 recites a purified DNA which encodes a substantially pure AGE-1 polypeptide that has at least 50% sequence indentity to the polypeptide of Seq ID No 1. Claim 9 recites a purified DNA comprising an AGE-1 nucleic acid sequence which is at least 30% identical to the nucleic acid sequence of Seq ID No 2.

In the currently written form, claim 8 is drawn to a purified DNA that encodes a substantially purified AGE-1 polypeptide. On page 4 of the specification, the term "substantially

pure" is defined as a preparation which is at least 60% by weight (dry weight) the compound of interest. The specification further states that the preparation is preferably at least 75%, more preferably at least 90%, and most preferably 99% pure, by weight. This would indicate that the purified AGE-1 polypeptide may have 1-25% of impurity or other polypeptides. Even when the polypeptide is 99% pure, it would contain 1% polypeptides of unknown nature, and when the preparation is 75% pure it will have 25% polypeptides of unknown nature. However, the specification discloses only Seq ID No.2 that encodes the AGE-1 polypeptide disclosed in Seq ID No. 1.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, it is Seq ID No.2. The specification does not provide any description of what other polynucleotides would have been that would have encoded for the polypeptides present in the substantially pure preparation of AGE-1 polypeptide and since the 1-25% of the polypeptides are impurity, their composition and nature may depend on the method of purification, therefore, there is no way of knowing what these impurities would be in any given preparation of the claimed polypeptide.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence). In the instant case, the only other identifying characteristics are the statement in the specification that AGE-1 protein is closely related to a family of mammalian PI 3- kinase p110 catalytic subunits (page 21, lines 8-10). Again, the specification does not provide any description as to what would be the characteristic of these polypeptides and whether any of these polypeptides would have been related to PI 3-kinase.

This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of cDNAs besides Seq ID No. 2 at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus.

7. Claims 8 -13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of claims 8 and 9 has been previously summarized in para 6 above. Claims 10 and 11, respectively, are drawn to a vector comprising the polynucleotides of claim 8 or 9 and to a cell comprising the purified DNA of claim 8 or 9. Claim 12 recites a method of producing recombinant AGE-1 polypeptide by transforming a cells with the DNA of claim 8 or 9 , culturing the transformed cell and isolating the recombinant peptide. Claim 13 is drawn to recombinant polypeptide produced according to the method of claim 12. Claim 15 recites a method of identifying a compound that decreases the expression of an AGE-1 gene wherein a cell expressing AGE-1 DNA of claim 8 or 9 is contacted with a candidate compound and AGE-1 gene expression is monitored.

The specification is not enabling for the claimed invention because the specification does not provide sufficient guidance as to how an artisan would have made all the claimed polynucleotide sequences, vectors, and host cells expressing all the claimed polynucleotide sequences and would have used those without undue experimentation.

As stated previously, in the currently written form, claim 8 is drawn to a purified DNA that encodes a substantially purified AGE-1 polypeptide. On page 4 of the specification, the term "substantially pure" is defined as a preparation which is at least 60% by weight (dry weight) the compound of interest. The specification further states that the preparation is preferably at least 75%, more preferably at least 90%, and most preferably 99% pure, by weight. This would indicate that the purified AGE-1 polypeptide may have 1-25% of impurity or other polypeptides. Even when the polypeptide is 99% pure, it would contain 1% polypeptides of unknown nature, and when the preparation is 75% pure it will have 25% polypeptides of unknown nature. However, the specification does not provide any guidance as to what these unknown polypeptides would have been and therefore, an artisan would not have known what nucleotide sequences would have encoded for the unknown polypeptides.

Additionally, in the currently written form, claim 8 and 9 encompass all the purified DNA sequences that would have been 30% identical to the nucleotide sequence of Seq ID No 2 in any number of nucleotides over the entire length of claimed Seq ID No. 2. However, the specification does not provide any guidance or example as to how would an artisan have made all these innumerable polynucleotides that encode these fragments or polypeptides, fusion proteins or precursor proteins or proteins with tags etc., and even if one had to assume that using various molecular biology techniques described in the specification in pages 26-27, an artisan would have been able to make these polynucleotides, would all the polypeptides encoded by the isolated polynucleotides have had any specific functions? In the absence of any function, what would have been the use of making all these polynucleotides, expression vectors comprising these polynucleotide segments, host cells comprising these polynucleotide expression vectors, producing the polypeptides encoded by these polynucleotides or preparing membranes of host cells expressing these polynucleotides? Furthermore, just because the claimed polypeptides have amino acid identity to a known protein, does not ensure that the polypeptide or its derived or cloned fragments would have the same function or even any function as that of the AGE-1 polypeptide. For example, the polynucleotide sequence disclosed in Seq ID No 2 has 50.6% best local similarity with the sequence of photoprotein aequorin (Genbank accession no Q04441, JO2096597A) over a region of 190 nucleotides. However, the specification does not provide any disclosure whether aequorin would have the AGE-1 activity or would have kinase activity. Additionally, if the artisan would not have known the function of the proteins, how could one have gone about identifying the compounds that would have modified the expression of these unknown genes or genes that would have encoded the innumerable number of polypeptides encompassed by the claimed invention?

It is, therefore, concluded that the specification as filed is not enabling for the claimed invention as filed and an artisan would not have been able to practice the invention without undue experimentation. Therefore, limitation of the scope of the invention to an isolated polynucleotide sequence that encodes the polypeptide of Seq ID No 1, a vector comprising such a polynucleotide and a recombinant host cell expressing the said vector and the process of producing proteins from the host cells expressing said vector is proper.

8. Claims 16-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 16 is directed to a method of identifying compounds that decrease AGE-1 activity wherein a cell expressing an AGE-1 polypeptide is contacted with a candidate compound, and a decrease in the activity of AGE-1 polypeptide is monitored for identifying the AGE-1 modulating compounds. Claim 17 recites that the AGE-1 peptide encoded by an AGE-1 gene includes an amino acid sequence that is at least 50% identical to the amino acid sequence of Seq ID No 1. Claim 18 recites that the AGE-1 polypeptide is from an animal. Claim 19 recites that the method of claim 16 is carried out in a nematode or another animal. Claim 20 recites that the method involves assaying AGE-1 activity.

The specification as filed is not enabling for the claimed invention because the specification does not provide any evidence as to (i) what is the activity of the AGE-1 polypeptide; (ii) if the activity of AGE-1 polypeptide is not known, how would an artisan have assayed the AGE-1 activity in vitro; (iii) whether the polypeptides, that would have had 50% identity with the polypeptide disclosed in Seq ID No 1, would have the activity of AGE-1 polypeptide; (iv) whether the AGE-1 polypeptide from animals would have had the same activity as the AGE-1 polypeptide disclosed in Seq ID No 1; (v) whether an artisan would have been able to carry out the claimed method in any animal or nematodes? The specification does not provide any guidance as to how an artisan would have dealt with these problems and therefore, an artisan would not have been able to make and use the invention as claimed without undue experimentation.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

First issue, is what is the activity of an AGE-1 polypeptide? The specification on page 21 in lines 8-10 discloses that AGE-1 protein is closely related to a family of mammalian PI 3-kinase p110 catalytic subunit. Later on the specification states that AGE-1 is 29.6% identical to mouse p110alpha, 29.8% identical to human p110 beta and 28% identical to human p110 gamma (see page 22 lines 6-25). However, the specification does not contain any disclosure as whether AGE-1 has a kinase activity. Only because a protein has 28-40% sequence similarity or identity to certain proteins does not indicate that the protein would have the function of the known protein. Furthermore, the relatedness of the claimed protein to PI 3-kinase is calculated based on the sequence analysis programs Gap and Blast. However, there are several parameters that would affect the result of the analysis by these algorithms, therefore, by changing the parameters of a search a different result can be obtained. For example, when a sequence is compared using BlastP, different parameters that can be changed are -G Cost to open a gap [Integer], default = 11; -E Cost to extend a gap [Integer], default = 1; -e Expectation value (E) [Real], default = 10.0; -W Word size, default is 11 for blastn, 3 for other programs. -v Number of one-line descriptions (V) [Integer], default = 100; -b Number of alignments to show (B) [Integer], default = 100. If any one of these parameters or a combination of parameters are changed, the percent identity between sequences to be compared may change. The specification does not provide any guidance as to what parameters would have been used to find the sequences that would have claimed indent or similarity with the sequences in the database and would have had the claimed activity.

In the currently written format, the claimed invention encompasses all the sequences that would have 50% identity with any given sequence over any length of sequence. For example, if 4 amino acids in a region of 8 amino acids are identical that would have been encompassed by the claimed invention. However, the specification does not provide any disclosure as to whether a protein which has 50% sequence identity over any 8 amino acids in a protein that has total 1146 amino acids would have the function of the claimed protein. For example, when AGE-1 polypeptide sequence (Genbank accession no U56101) was compared by BlastP using default settings, 70 KD heat shock protein 6 (Genbank accession no p17066) showed a 27% identity over a region of 74 amino acids. However, the specification does not disclose if HSP70 KD protein would have the same activity as the claimed protein or vice versa. Likewise, enzyme

Isocitrate Dehydrogenase (Genbank accession no p33197) has 39% identity over a region of 41 amino acids, however, if only regions of 8 amino acids are compared, there would be 50% identity. The specification, however, does not provide any guidance as to whether claimed protein would have the activity of Isocitrate dehydrogenase, and whether the activity of the claimed protein could be assayed by using the conditions of Isocitrate dehydrogenase.

The specification on page 32, lines 14-21 discloses that the kinase activity of the AGE-1 peptide can be assayed by any standard assay, e.g. by measuring the ability of the enzyme to transfer radiolabeled Phosphate to a PIP substrate. However, the specification does not provide any guidance as to whether purification of the enzyme will be necessary to get any reliable or specific activity of the claimed protein because a crude extract may contain many kinases and kinase inhibitors. Furthermore, the specification does not provide any guidance as to whether a recombinant protein made from the disclosed Seq ID No 2 will be active in vivo because it is art recognized that recombinant enzymic proteins produced in bacteria may not be enzymatically active due to the lack of post-translational modification machinery in bacterial cells. The specification does not provide any guidance as to whether the claimed protein would have required any post-translation modification for its activity.

The specification in the currently written format, encompasses the AGE-1 polypeptides from all the animals, however, the specification does not provide any guidance as to whether the AGE-1 polypeptides from all animals would have the same functions. It is known in the art that two proteins from different species or even proteins that have similar function in different animals or organisms, even belonging to same family, may have very divergent function, because a protein or enzyme may require several other protein or other co-factors for its activity. For example, retroviruses have RNA binding proteins which have motifs that direct them to nucleus. HIV-1 has two such proteins which have RNA binding domains and nuclear localization signals that import these proteins to nucleus, however, their RNA binding activities as well as the interaction of their nuclear localization signals with other proteins is very different (see pages 102-106 in Clements JE et al Clinical Microbiology Reviews 9:100-117, 1996). Therefore, only because a protein belongs to a family of proteins, does not necessarily mean that the protein would have same activity, particularly when proteins are from different species.

The specification does not disclose any method how will it carry out the claimed method in a nematode or any other animal that would have the AGE-1 gene. The specification on pages 7-10 describe the method of studying the effect of mutant genes on the growth of the worms, for example, worms homozygous or heterozygous for a certain gene are mated to produce a progeny that would have a certain genetic makeup in terms of carrying mutations in a gene. However, these assays are not based on systems where a single isolated DNA, that encodes for a certain protein, is used to study the activity of a gene. Furthermore, these genetic assays monitor a trait and the development of a certain trait may depend on the concerted actions of multiple gene products. Therefore, a skilled artisan would not be able to determine whether the changes in a genetic trait are due to the change in the function of one gene. The specification provides prophetic examples of methods of screening for compounds in vitro. The specification does not provide any guidance as to the method used in animals, for example, in a mouse or any other animal, except for the examples provided for the methods of genetic analysis in nematodes. The specification does not provide any disclosure as to how the gene encoding the AGE-1 peptide will be introduced in the nematodes or any other animal and the assay of the activity will be performed in an animal.

In conclusion, the specification is not enabling for the claimed invention because the specification does not provide any suitable guidance as to (i) what is the activity of the AGE-1 polypeptide; (ii) if the activity of AGE-1 polypeptide is not known, how would an artisan have assayed the AGE-1 activity in vitro; (iii) whether the polypeptides, that would have had 50% identity with the polypeptide disclosed in Seq ID No 1, would have the activity of AGE-1 polypeptide; (iv) whether the AGE-1 polypeptide from animals would have had the same activity as the AGE-1 polypeptide disclosed in Seq ID No 1; (v) whether an artisan would have been able to carry out the claimed method in any animal or nematodes? In conclusion, the specification does not provide any guidance as to how an artisan would have dealt with these problems and therefore, an artisan would not have been able to make and use the invention as claimed without undue experimentation.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 9 is indefinite because it is unclear which parameters of Gap and Blast analysis are to be used to calculate % identity.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Hiles et al 1992 (Genbank accession no A43322; Cell 70:419-429, 1992).

The invention of claim 8 and 9 has been previously described in para 6 above.

Hiles et al teach the sequence of 110 KD catalytic subunit of PI 3-kinase, its structure and expression. The nucleotide sequence taught by Hiles et al shows 45.9% best local similarity to the claimed nucleotide sequences of Seq ID No 2, whereas the amino acid sequence taught by Hiles et al has 30.7% best local similarity to the sequence disclosed in Seq ID No 1. Furthermore, when sequences in smaller regions of 8-10 nucleotides or 5-6 amino acids are considered, there is almost 100% indent (see amino acids 1011-1018 of the claimed amino acid sequence or nucleotides 2675-2793 of the claimed polynucleotide sequences) Therefore, the nucleotides sequence claimed in claims 8 and 9 are anticipated by Hiles et al.

13. Claims 8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Goode et al (Genbank accession no R46294; WO9403609, 1994).

The invention of claims 8 and 9 has been summarized in para 6 above.

Goode et al teach eukaryotic cells transformed with mammalian phospholipid or protein kinase DNA-useful in assays for compounds in cell growth regulation and treating cancer. The amino acid sequence taught by Goode et al has over 30% sequence similarity with the claimed amino acid sequence disclosed in Seq ID No 1. The nucleotide sequence taught by Goode et al has 46% similarity with the nucleotide sequence claimed in Seq ID No 2. Therefore, the nucleotide sequence encoding Seq ID No 1 and the nucleotide sequence disclosed in Seq ID No 2 are anticipated by Goode et al.

14. Claims 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Wilson et al (Genbank accession no Z66519 Nature 368:32-38, 1994).

The invention of claim 9 has been summarized in para 6 above.

Hiles et al teach 2.2 MB sequence chromosome III of C. elegans. There is best local similarity of 96% between the sequence disclosed by Wilson et al and the sequence disclosed in Seq ID No 2, over a range of 150 nucleotides. There is 100% sequence similarity in a region of 100 nt. Therefore, the nucleotides sequence claimed in claims 9 are anticipated by Wilson et al 1994.

15. Claims 10-13 and 15-20 are free of prior art because they are drawn to a nucleic acid of AGE-1 protein, a host cell expressing the claimed nucleotides and assay methods for identifying compounds that modulate AGE-1 polypeptides. The prior art by Morris et al 1996 (Morris JZ et al Nature 382:536-539, 1996) is made of record because it discloses the nucleotide sequences of AGE-1 and suggest that AGE-1 is a member of PI 3-kinase.

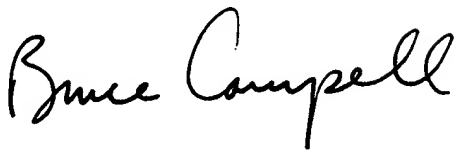
16. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Stanton, can be reached on (703) 308-2801. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Ram R. Shukla, Ph.D.



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